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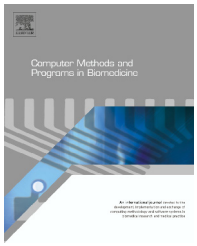

Predicting healthy older adult's brain age based on structural connectivity networks using artificial neural networks

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ABSTRACT

Brain ageing is followed by changes of the connectivity of white matter (WM) and changes of the grey matter (GM) concentration. Neurodegenerative disease is more vulnerable to an accelerated brain ageing, which is associated with prospective cognitive decline and disease severity. Accurate detection of accelerated ageing based on brain network analysis has a great potential for early interventions designed to hinder atypical brain changes. To capture the brain ageing, we proposed a novel computational approach for modeling the 112 normal older subjects (aged 50–79 years) brain age by connectivity analyses of networks of the brain. Our proposed method applied principal component analysis (PCA) to reduce the redundancy in network topological parameters. Back propagation artificial neural network (BPANN) improved by hybrid genetic algorithm (GA) and Levenberg–Marquardt (LM) algorithm is established to model the relation among principal components (PCs) and brain age. The predicted brain age is strongly correlated with chronological age ($r = 0.8$). The model has mean absolute error (MAE) of 4.29 years. Therefore, we believe the method can provide a possible way to quantitatively describe the typical and atypical network organization of human brain and serve as a biomarker for presymptomatic detection of neurodegenerative diseases in the future.

1. Introduction

Because of increasing longevity and declining fertility, the proportion of the world's older adults will double from about 11% to 22% between 2000 and 2050. Cognitive health has consistently been cited as a key cause for quality of life [1] and as an important contributor to late-life functioning [2,3]. A recent study [4] suggests that people in younger brain age compared to their chronological age would have less social and economic burden. Maintaining a healthy brain is the key factor in preserving the quality of life for older people. Therefore, understanding the pattern of healthy brain ageing is important to freeze the effects of brain ageing and possibly extends healthy cognitive for our ageing society.

Brain ageing is a complex and inevitable biological process associated with dysfunction in cognition, neural function, and brain structure. For those older people, there are considerable

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individual differences of preserving cognitive functions. This heterogeneity has been suggested to reflect a continuum extending from "successful cognitive ageing" [5], with high levels of functioning throughout the lifespan, to "advanced ageing" [6,7], the possibility of individuals suffering from memory impairment and neurodegenerative diseases, such as Alzheimer's disease (AD). It has become increasingly obvious that neurodegenerative disease exists in subtle preclinical forms for many years before the symptom onset [8,9]. Early disease-related brain changes may represent the early stage of neurodegenerative diseases rather than normal concomitants of ageing, even without any clinical symptoms [10]. Early AD patients showed signs of accelerated brain ageing (+10 years) [11]. Noninsulin-dependent diabetes mellitus subjects have an older brain compared with their chronological age (+4.6 years) [12]. Hypertension subjects have estimated brain age older than their chronological age (+4.1 years)[13]. Koutsouleris et al. [14] found that schizophrenia has an accelerated ageing effect (+5.5 years). Accelerated ageing effect may also extend to other mental disorders (major depression (+4.0 years), borderline personality disorder (+3.1 years), and at-risk mental states for psychosis groups (+1.7 years)). Therefore, a prediction model of brain age can detect the subtle brain deviations from the normal ageing pattern, before the pathological onset. If the predicted brain age according to brain images is older than the subject's chronological age, then this could be the evidence of accelerated brain ageing.

The human brain is a network of interconnected structural and functional brain regions. Current neuroimaging techniques allow us to map anatomical regions as well as their interconnecting pathways. The set of connections in this complex neural network, called the Connectome [15,16], has been the focus in recent years because of advances in neuroimaging technique and network analysis methods. The Human Connectome Project (HCP) [17,18] was launched in 2009 as a 5-year effort to characterize brain anatomical and functional connectivity in healthy adults. Ageing is not only a major risk factor for human cognition, but also a predictor of conversion to other neurodegenerative diseases. Ageing might influence a set of brain regions; each region could affect brain dynamics by altering its own activity pattern, the pattern of direct connected neighbors of the region, the activity in the rest of the brain regions, and the whole-brain network.

Advances in diffusion tensor imaging (DTI) allow us to infer subject specific brain connectivity in vivo. In this study, we employed DTI to explore the topological changes of whole-brain WM structural connectivity in the normal older subjects. This study hypothesized that: when healthy people are ageing, they will show a topological pattern revealed by characteristics in the WM networks. Moreover, these topological changes can be regarded as the biomarkers to predict brain ageing, which will benefit our understanding of cognitive ageing and neurodegenerative diseases. Here, we used DTI tractography to build the human brain WM networks of 112 healthy ageing subjects, followed by a graph theoretical analysis. Principal component analysis (PCA) was integrated with back propagation artificial neural network (BPANN) to predict the brain age. Using principal components (PCs) as BPANN's input can eliminate redundancies of original network metrics and remove the correlation between them. To improve the performance of the BPANN and reduce the necessary training time, a hybrid optimization algorithm that integrates both genetic algorithm (GA) and Levenberg–Marquardt (LM) algorithm is used.

2. Materials and methods

2.1. Clinical cases

One hundred and twelve right-handed healthy older volunteers participated in this study. Subjects were recruited by advertisement in local newspapers and campus flyers. The research was approved by the university ethics committee, and all subjects provided written informed consent before participating in the study. The participants were contacted by telephone and underwent a preliminary telephone screen for eligibility. Exclusion criteria consisted of left-handedness, current or past history of alcohol or drug use disorder, neurological and psychiatric disorders, and the presence of ferrous metal implants. After passing the telephone screen, participants were scheduled for a more detailed cognitive evaluation. The subjects are eligible to participate in the study if (a) they do not meet research NINCDS-ADRDA criteria of a diagnosis of probable AD or DSM-IV criteria for any type of dementia or research criteria for mild cognitive impairment (MCI); (b) they have a Folstein MMSE score $\geq$26; (c) they have a 17-item Hamilton Depression Rating Scale (HAMD-17) score $\leq$10. All subject characteristics are shown in Table 1.

All subjects were asked to answer a MRI safety questionnaire and remove MRI-incompatible objects during pre-MRI safety screening. MRI scans were performed on a 3-Tesla (3 T) Signa II scanner (General Electric Medical Systems, Milwaukee, WI) using an eight-channel phased array head coil. The T1-weighted ($T1_W$) data were acquired using 3D spoiled gradient echo (3DSPGR) sequence with the following parameters (204 slices, 1 mm thickness, TR = 5.3 ms, TE = 2.0 ms, TI = 500, flip angle = 15°, matrix = 256 × 256, FOV = 256 mm × 256 mm). The DTI data were acquired using a single-shot spin echo diffusion sensitized echo-planar imaging (EPI) sequence (58 slices, 2.6 mm thickness, TR = 12.5 s, TE = 71 ms, 51 diffusion encoding gradients, b = 1000 s/mm^2, NEX = 2, matrix = 128 × 128, FOV = 250 mm × 250 mm and eight non-diffusion volumes).

2.2. Image preprocessing

$T1_W$ MRI were preprocessed using Statistical Parametric Mapping software (SPM8, Welcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm)

Table 1 – Study population characteristics (N = 112).

Characteristics	N or mean ± SD	% or range
Age (years)	67.5 ± 7.2	50.4–79.1
Sex		
Male	54	48.2%
Female	58	51.8%
Education (years)	16.8 ± 2.1	9–21
HAMD-17	2.4 ± 2.7	0–8
MMSE	29.0 ± 0.7	26–30

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